Reply

We thank Drs. Guazzi and Bandera for their thoughtful comments in which they assert the value of incorporating multiple variables from cardiopulmonary exercise (CPX) testing to best reflect the complex pathophysiology of chronic heart failure (HF) and thereby maximize its prognostic value. We agree with this concept, and even made a similar point in our paper, "Oscillatory expiratory breathing, end-tidal partial pressure of carbon dioxide, VE/VO_2 ratios, recovery gas exchange dynamics, and heart rate and blood pressure responses are among an extensive array of CPX assessments that can be used to enhance prognostic assessment" (1). Unfortunately, these additional gas exchange variables were not collected as part of the HF-ACTION (Heart Failure–A Randomized Controlled Trial Investigating Outcomes of Exercise Training) trial database.

Drs. Guazzi and Bandera also state that EOV has been "proven prognostically superior" to both peak VO_2 and VE/VCO_2 slope as well as the 6MWT. However, this assertion seems primarily based upon their single center study of 253 patients, which included both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) subgroups (2). In contrast, HF-ACTION included 2,054 patients from over 70 sites, all with HFrEF, and with a much larger number of events. Furthermore, the 6MWT protocol used in Guazzi's reference was based on stride length and number of steps taken (which assumed that stride length did not change as patients fatigued), which is considerably different from the standardized and validated 6MWT protocol used in HF-ACTION (1). These differences likely account for the better prognostic performance of the 6MWT in HF-ACTION.

Measurement of EOV relies on variations of minute ventilation over time, which are usually assessed qualitatively from graphs, with inherent ambiguity regarding classification amidst normal fluctuations associated with breath-to-breath ventilation during exercise. In contrast, 6MW distance is a simple measure that can be readily incorporated into clinical practice and trials without specialized equipment, and which is reproducible as long as a standardized test protocol is used.

To summarize, we agree with Drs. Guazzi and Bandera regarding the undisputed utility of CPX for providing pathophysiological insights and prognostic assessments in patients with HF, and also for its multiple unique diagnostic applications. However, our analysis indicates that the 6MWT also has significant value, both in respect to prognostic sensitivity as well as its relative convenience.

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http://dx.doi.org/10.1016/j.jacc.2013.02.028

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Hypothermia: Is it Good for the Brain and Not for the Arteries?

I read with interest the research correspondence letter by Penela et al. (1). As pointed out by the authors, the protocol for induced hypothermia is designed to reduce the temperature of the patient to 32°C to 34°C for up to 24 h. The results of this form of therapy are summarized in the *Annals of Neurology* (2). Up to two-thirds of patients receiving hypothermia therapy might go home with good function, but recovery of higher intellectual faculties has not been well-studied, and nothing is reported about the effects of hypothermia on atherosclerotic vessels in these patients.

As far as I can tell, no one has considered what the effects of induced hypothermia are on atherosclerotic lesions either in the cerebral or coronary circulation.

Several years ago, Vedre et al. (3) reported that local factors might play an important role in triggering plaque rupture. One of these factors was temperature. They showed that cholesterol crystallizes from a liquid to a solid form and forms sharp-tipped crystals that expand in volume by up to 45%. In vitro experiments documented that there was a significant difference in the change of volume expansion of cholesterol between 34°C and 37°C.

In the human, it is theoretically possible that crystallization of cholesterol at low temperatures at approximately 34°C might be sufficient to trigger cholesterol crystallization, especially in combination with other physical factors. Because all of these patients very likely have atherosclerotic plaques in the coronary circulation and perhaps the cerebral circulation as well, rupture of atherosclerotic plaques might be triggered by the formation of sharp-tipped cholesterol crystals. Thus, it is possible that cooling the patient to 34°C or less could potentially worsen the vascular stenoses by sharp-crystallized cholesterol disrupting plaques or, as the authors point out, "activation of platelets" might be responsible for thrombosis despite treating with clopidogrel (because hypothermia might decrease metabolism of cholesterol to its active form). Thus, it is important to consider the possibility that lowering temperature to prevent brain ischemia or brain infarction might in fact be detrimental to coronary and cerebral vessels, both from the standpoint of disrupting plaques and thrombosis occurring in patients with stents.

Hypothermia might buttress the clinical evidence that myocardial infarction and unstable angina syndromes occur more frequently in cold weather and during early morning hours when body temperature is slightly lower in most patients. Interestingly, platelet activation apparently occurs in the morning hours as well.

I certainly agree that the evidence favors lowering body temperature to diminish ischemic brain damage, but it is possible, on the basis of the work of Vedre et al. (3) and Penela et al. (1), that

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cooling the patient to 34°C might do something detrimental to the vasculature.

I share the concern of the authors that these observations require further study, because hypothermia might result in untoward effects not perceived by the early proponents of this therapy.

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http://dx.doi.org/10.1016/j.jacc.2013.02.034

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